UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/689,430	10/12/2000	Christopher E. Walsh	35052/204373 (5052-53)	7095

826 7590 12/12/2001

ALSTON & BIRD LLP
BANK OF AMERICA PLAZA
101 SOUTH TRYON STREET, SUITE 4000
CHARLOTTE, NC 28280-4000

EXAMINER	
LI, QIAN J	

ART UNIT	PAPER NUMBER
1632	8

DATE MAILED: 12/12/2001

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/689,430	Applicant(s) WALSH ET AL.	
	Examiner Janice Li	Art Unit 1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-67 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-63,65 and 67 is/are rejected.

7)☒ Claim(s) 64 and 66 is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 4,5 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claims 1-67 are pending and under current examination.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 18, 19 and 35 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The methodology for determining adequacy of Written Description to convey that applicant was in possession of the claimed invention includes determining whether the application describes an actual reduction to practice, determining whether the invention is complete as evidenced by drawings, or determining whether the invention has been set forth in terms of distinguishing identifying characteristics as evidenced by other descriptions of the invention that are sufficiently detailed to show that applicant was in possession of the claimed invention (*Guidelines for Examination of Patent Applications under 35 U.S.C. § 112, p 1 "Written Description" Requirement;* Federal Register/ Vol 66. No. 4, Friday, January 5, 2001; II Methodology for Determining Adequacy of Written Description (3.)).

These claims are directed to a rAAV comprising a heterologous sequence encoding a B-domain deleted factor VIII selected from the group consisting of a sequence that hybridizes to nucleotides 419-4835 of the SEQ ID No: 1 under conditions of high stringency.

With respect to claims limiting a polynucleotide by hybridization conditions, even under relatively high stringent conditions, the claimed nucleotide sequence could hybridize to a genus of polynucleotides that are similar, but not identical to the recited polynucleotides. This genus embraces sub-sequences that are unknown and unsequenced polynucleotides, which may not encode a functional Factor VIII or which may generate an amino acid sequence that is irrelevant to the recited Factor VIII.

The limitation by hybridization is obvious generic to a considerable number of nucleotides varying in the length of the nucleic acids, the degree of homologies among the sequences, and the biological activities of the encoded polypeptides. The specification fails to provide an adequate description to teach the structure-function relationship of these polypeptides with regard to their function as biologically active factor VIII, and accordingly does not provide a reasonable guide for those seeking to practice the invention.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The

specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116).

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

In view of these considerations, a skilled artisan would not have viewed the teachings of the specification as sufficient to show that the applicant was in possession of the claimed invention commensurate to its scope, therefore, only the described 419-4835 of the SEQ ID No: 1 and variants due to the degeneracy of the genetic code meet the written description provision of 35 U.S.C. §112, first paragraph.

Claims 18, 19, and 35 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making and using a rAAV vector comprising a heterologous nucleotide sequence encoding a B-domain deleted factor VIII, wherein the said sequence is selected from the group consisting of a sequence given as nucleotides 419-4835 of the SEQ ID No: 1 or differs from nucleotides 419-4835 of the SEQ ID No: 1 due to the degeneracy of the genetic code, does not reasonably provide enablement for making and using a rAAV vector comprising a heterologous nucleotide sequence encoding a B-domain deleted factor VIII, wherein the said sequence is selected from the group consisting of a sequence that *hybridizes* to nucleotides 419-4835 of the SEQ ID No: 1 under conditions of high stringency, or differs

from the complement sequence due to the degeneracy of the genetic code. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

There are many factors to be considered when determining whether the disclosure satisfies the enablement requirements and whether undue experimentation would be required to make and use the claimed invention (see *In re Wands*, 858 F. 2d 731, 737, 8 USPQ 2d 1400, 1404, 1988). These factors include but are not limited to the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability of the art, the breadth of the claims, and amount of direction provided.

As discussed above, these claims embrace a considerable number of nucleotides varying in the length of the nucleic acids, the degree of homologies among the sequences, and the biological activities of the encoded polypeptides, and the specification fails to provide an adequate written description to teach the structure-function relationship of the recited polypeptides with regard to their function as biologically active factor VIII, and thus fails to provide a reasonable guide for those seeking to practice the invention. Therefore, in view of the limited guidance, the lack of predictability of the art and the breadth of the claims, it would have required undue experimentation by the skilled artisan to practice the invention as it is broadly claimed.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claims 1, 3-18, 20-63, 65, and 67 are rejected under 35 U.S.C. 102(e) as being anticipated by *Couto et al* (US 6,221,349), and as evidenced by *Ill et al* (US 5,744,326).

These claims are directed to a recombinant adeno-associated vector (rAAV) comprising a heterologous nucleotide sequence encoding B-domain deleted factor VIII operably linked with at least one enhancer and promoter, wherein said B-domain deleted factor VIII comprising the amino acid sequence set forth in SEQ ID No: 2; wherein the rAAV is selected from the group consisting of serotypes 1-5 of AAV; wherein the factor VIII is operably linked with a liver-preferred expression control element, such as the hepatitis B virus Enhl enhancer comprising the sequence given as about nucleotide 419-4835 of the SEQ ID No: 1, and further comprising at least one transcription factor binding site, such as HNF3; wherein the promoter is an AAV ITR; wherein the rAAV vector is in a pharmaceutically acceptable carrier; wherein the liver specific promoter is the mouse albumin promoter; wherein the heterologous sequence further comprises a polyadenylation sequence comprising the sequence given as about nucleotides 150-4914 of the SEQ ID No: 1; wherein the heterologous nucleotede sequence of the rAAV is selected from the group consisting of a nucleotide sequence that hybridizes under high stringency condition to 419-4835 of the SEQ ID No: 1. The

claims further pertain to methods of delivering the aforementioned rAAV to a cell comprising contacting the cell with the vector *in vitro* or administering it to cells in a mammalian subject, preferably human; wherein the cells are preferably human liver cells; wherein the routes of administration is selected from oral, transdermal, transmucosal, intravenous, subcutaneous, intramuscular etc. Claims are also drawn to a method of producing a high-titer stock of the rAAV, and the viral stock, host cells produced.

Couto et al teach a rAAV encoding a B-domain deleted factor VIII (column 3, lines 54-56) operably linked with a liver-specific promoter, such as albumin promoter (column 10, lines 11-23), and the hepatitis B virus Enhl enhancer (note: although *Couto et al* do not particularly recite the enhancer, but the instant claims 12 & 28 define the enhancer as "given as about nucleotides 419-4835 of the SEQ ID No: 1", which embrace the SEQ ID Nos: 13 and 14 of *Couto et al* having 97.8% sequence identity with 419-4835 of the SEQ ID No: 1). SEQ ID Nos: 13 and 14 of *Coute et al* have 99% of sequence identity with 419-4835 of the SEQ ID No: 1, and have 90.9% sequence identity, and 99% best local similarity with 150-4914 of the SEQ ID No: 1, therefore will hybridize with said sequences and meet the claim limitation set forth as "given as about". The constructs of *Couto et al* further comprises an AAV ITR promoter (figures 3 & 4, column 6, line 35), a HNF3 binding site, a polyadenylation sequence (column 4, line 4, column 10, lines 32-52). *Coute et al* go on to teach that AAV serotypes 1-5 and 7 could be used (column 6, lines 19-20), and both *ex vivo* and *in vivo* delivery methods (columns 19-20, claims 1-25). They teach that the route of *in vivo* delivery of rAAV is not to be limited to any particular route of

administration, but the preferred route of delivery is via the portal or arterial vasculature (column 4, lines 17-19), and muscle cells (column 19, line 63). *Coute et al* also teach a method of producing rAAV stock comprising the steps of claim 55 (columns 15 and 17), and pharmaceutical carriers for delivery of the vectors (columns 17-19).

Claims 5, 17, 33, 48, 49 are drawn to a B-domain deleted factor VIII having SEQ ID No:2. Although *Couto et al* do not particularly disclose SEQ ID No: 2, since the B-domain of factor VIII is well known in the art as evidenced by *Ill et al*, who disclose a B-domain deleted Factor VIII (SEQ ID No:2, column 4, lines 26-27) having 99.8% sequence identity and 99.9% best local similarity with the instant SEQ ID No: 2. Thus, in the absence of evidence to the contrary, the Office assumes that the recited B-domain deleted Factor VIII in the cited patent and that of the instant application have the same amino acid sequence, or differ due to the genetic code degeneracy or other technical reasons.

Thus, *Couto et al* anticipate the instant claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-63, 65, and 67 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Couto et al* (US 6,221,349) as applied to claims 1, 3-18, 20-63, 65, and 67 above, and further in view of *GAO et al* (US 6,258,595).

Claims 2 and 19 are further directed to a DNA spacer in the rAAV construct, *Couto et al* fail to teach such a spacer. However, before the instant application was filed, *Gao et al* teach to include a DNA spacer in the construct of recombinant AAV vector as an optional element in the design of the AAV vector (the paragraph bridging columns 12 and 13).

Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the vector taught by *Couto et al,* by simply including a DNA spacer in the vector construct as taught by *Gao et al.* The ordinary skilled artisan would have been motivated to modify the claimed invention to improve the expression capacity of the rAAV vector with a reasonable expectation of success. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Claim Objections

Claim 43 is objected to because the improper dependency.

Claims 64 and 66 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Q. Janice Li whose telephone number is 703-308-7942. The examiner can normally be reached on 8:30 am - 5 p.m., Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Karen M Hauda can be reached on 703-305-6608. The fax numbers for the organization where this application or proceeding is assigned are 703-308-8724 for regular communications and 703-308-4242 for After Final communications.

Any inquiry of formal matters can be directed to the patent analyst, Kay Pinkney, whose telephone number is (703) 305-3553.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235. The faxing of such papers must conform to the notice published in the Official Gazette 1096 OG 30 (November 15, 1989).

Q. Janice Li
Examiner
Art Unit 1632

QJL
November 26, 2001

JAMES KETTER
PRIMARY EXAMINER